Standard dose alectinib versus Therapeutic Drug Monitoring guided alectinib dosing

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24311

Source
NTR

Brief title
Adapt Alec Trial

Health condition

ALK fusion in stage IV NSCLC

Sponsors and support

Primary sponsor: University Medical Center Groningen
Source(s) of monetary or material Support: UMCG

Intervention

Outcome measures

Primary outcome

The primary endpoint is a a prolonged mPFS in the TDM-guided dosing arm for the subgroup who had a Cmin < 435 ng/mL at a certain time point during treatment, compared to these patients in the fixed dosing arm

Secondary outcome

1. Feasibility and tolerability of TDM. This will be measured as percentage of successful TDM measures, in which successful is defined as target attainment with manageable toxicity.
2. Overall response rates (ORR). ORR will be defined as partial response or complete response (according to RECIST v1.1) percentage of the total treated population.
3. Median overall survival (mOS). OS will be defined as the time from randomization to death from any cause in the total population
4. Patient adherence. This will be measured by the amount of drugs that are taken by the patients diary.
5. Physician adherence. This will be measured as the percentage of dose recommendations that is implemented by the treating physicians.
6. Toxicity related to the plasma concentration and dose increases. This will be defined as AE's in the subgroups with Cmin < 435 ng/mL and all Cmin ≥ 435 ng/mL, and in patients who did and who did not receive a PK-guided dose increase.

Study description

Background summary

Currently, over 40% of all recently approved oncolytics are oral agents.1 Compared with the more traditional intravenous therapies, these oral agents are less invasive and more patient friendly. On the other hand, due to home administration, patient's adherence could be compromised.2 Secondly, the oral administration route makes these agents more prone to drug-drug and drug-food interactions, both resulting in suboptimal drug exposure, with rates varying between only 30% and 70% of desired drug exposure targets.3 Notably, overdosing causes unnecessary and preventable side effects, while underdosing results in reduced effects and tumour growth.
In lung cancer patients treatment with EGFR-TKI has been shown to be influenced by e.g. body weight and renal impairment. Adapting the EGFR-TKI dose could help in preventing major side effects and improve outcome of the treatment4. For ALK-TKI this has not been studied largely yet.
Despite the relative short treatment period of on average a year, and the severity of the disease, still 20% of lung cancer patients have suboptimal adherence.5 This may partly help to explain why survival of patients with metastatic non-small cell lung carcinoma (NSCLC) in real-world daily practice is nearly one quarter shorter than for patients included in clinical trials.6 Adherence is the single most modifiable risk factor that comprises treatment outcomes but is difficult to measure and no studies so far have employed objective methods. Objective, long-term adherence data can support patients' self-management in the outpatient setting, allows enhanced physician clinical decision making and informs therapeutic drug monitoring (TDM) targets (dose increase or decrease).
Alectinib is used in first and second line settings in ALK positive advanced lung cancer as standard of care.7 Groenland et al. found in an exposure-response analysis of alectinib a median alectinib Cmin of 517 ng/mL (range: 141-1944 ng/mL), with an interindividual

variability of 57%. In total, 37% of the patients had a median Cmin< 435 ng/mL. The median PFS was 12.8 months vs. not estimated (95%CI: 19.8 months – not estimated) for patients with Cmin below or above 435 ng/mL, respectively (p=0.04, log-rank) (Figure 1). Multivariable analysis corrected for WHO performance status and prior treatment with ALK-inhibitor(s) resulted in hazard ratio of 4.29 (95%CI: 1.33-13.90, p=0.015) in favour of patients with higher drug exposure.8
Therefore, patients should have an alectinib Cmin ≥ 435 ng/mL, which could be established by therapeutic drug monitoring (i.e. adjusting the dose based on measured drug concentrations). Taken together, we hypothesize that the PFS will increase by more than 10 months comparing therapeutic drug monitoring (TDM) and increasing the dose of alectinib if the Cmin threshold of 435 ng/mL is not reached and with fixed alectinib dosing.

Study objective

In lung cancer patients treatment with EGFR-TKI has been shown to be influenced by e.g. body weight and renal impairment. Adapting the EGFR-TKI dose could help in preventing major side effects and improve outcome of the treatment4. For ALK-TKI this has not been studied largely yet.

Study design

at regular visits (4,8 and every 8 weeks thereafter)

Intervention

ECG, bloodsampling, scans, optional biopsy

Contacts

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Eligibility criteria

Inclusion criteria

1. Patients with locally advanced or metastatic NSCLC (stage IIIB to stage IV by AJCC 8th)

2. Male or female ≥18 years old

3. ECOG Performance Status of 0−2

4. Histologically or cytology confirmed NSCLC

5. Documented ALK rearrangement based on an EMA approved test

6. Patients can either be chemotherapy-naïve or have received one line of platinum-based chemotherapy

7. Patients with brain or leptomeningeal metastases are allowed on study if the lesions are asymptomatic without neurological signs and clinically stable for at least 2 weeks without steroid treatment. Patients who do not meet these criteria are not eligible for the study. However, they can be re-screened after completing WBRT or gamma –knife treatment. They must have completed any corticosteroid therapy ≥2 weeks prior to the first dose of study treatment.

8. Measurable disease (by RECIST criteria version 1.1) prior to the first dose of study treatment

9. Signed written Institutional Review Board (IRB)/Ethical Committee (EC) approved informed consent form, prior to performing any study-related procedures.

Exclusion criteria

1. Any significant concomitant disease determined by the investigator to be potentially aggravated by the investigational drug

2. Consumption of agents which modulate CYP3A4 or agents with potential QT prolonging effects within 14 days prior to admission and during the study (see concomitant medication restrictions)

3. Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or absorption of oral medications, or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the subject in this study.

4. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	23-03-2022
Enrollment:	196
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Plan description
undicided

Ethics review

Positive opinion

Date:	26-04-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL9441
Other	METc UMCG : METc 202000251

Study results

Summary results
NA